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Four-Dimensional Imaging and Radiation Therapy: A Review of Challenges and Advancements in Clinical Practices

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Abstract

4-Dimensional Radiation therapy (4DRT) has been vastly developed in the past two decades. Motion management has become a vital part of high precision radiotherapy, wherein Stereotactic Body Radiation Therapy (SBRT) turns out to be a great boon for treating thoracic and abdominal tumours with confidence. In this review paper, we have analyzed the development of motion management strategies and the advancement of 4DRT.We have discussed the evolution of Internal target volume (ITV), 4D imaging techniques and the problems of breathing motion. In the second part, we have discussed various methods to tackle breathing motion. We also have reviewed the dosimetric aspects of 4D imaging and its clinical implications. In the last section, we have elaborated the 4D radiation therapy and recent advancements and practices.

Keywords: *Motion management, thoracic tumours, breath-hold, 4-dimensional imaging, gating, respiratory tracking.*

1. Introduction

This review gives a brief introduction of development of imaging techniques at various levels and its adaptation to radiation therapy. We have also discussed the 4D scanning techniques of Magnetic resonance imaging (MRI) and Positron emission tomography (PET) systems. In the next session, we have discussed the motion management systems and its challenges for 4D imaging which is utilized for radiation therapy. In the final section we have discussed the 4D image utilization for radiation treatment, dosimetry aspects of a moving target and its implications on the treatment delivery.

Need for motion management

Respiratory motion is unique for every patient but predictable.[1] The characteristic of respiratory motion for every patient varies with amplitude between two fractions and during each treatment.[2] Hence the respiratory behavior cannot be presumed for any patient prior to 4D imaging. Lung motion is associated with the size of the tumor, the location of the tumor and diaphragm motion. [3-5] The tumor motion is highest in superior-inferior direction and smallest in the lateral and anterior-posterior direction.[6] The largest range of tumor motion in the lung is 5cm, whereas the abdominal organs such as the kidney, liver typically have more than 1cm.

Concept of ITV in motion management

Voluntary and involuntary motion of patients during the imaging is the major problem to obtain high quality images. High precision radiotherapy such as intensity modulated radiation therapy (IMRT), image guided radiation therapy (IGRT), adaptive radiotherapy (ART) requires high-fidelity image sequences without or minimal artifacts.[7] It is understood that the target is constantly moving and this has to be accounted for during treatment planning especially for cancers of the thorax and abdomen. An adequate, additional margin must be defined to the clinical target volume (CTV) in order to cover the target and spare the organs at risk (OARs) simultaneously. The International Commission on Radiation Units and Measurements (ICRU) 62 has introduced the concept of internal target volume (ITV).[8] Concept of ITV generation is shown in figure 1. It accounts for geometric uncertainties of organ motions which includes movement of bowel, heartbeat or respiration. It also accounts for changes in tumor size and shape. ITV is the union of gross tumor motion of the entire breathing cycle and this reduces the uncertainty during the treatment planning and delivery.

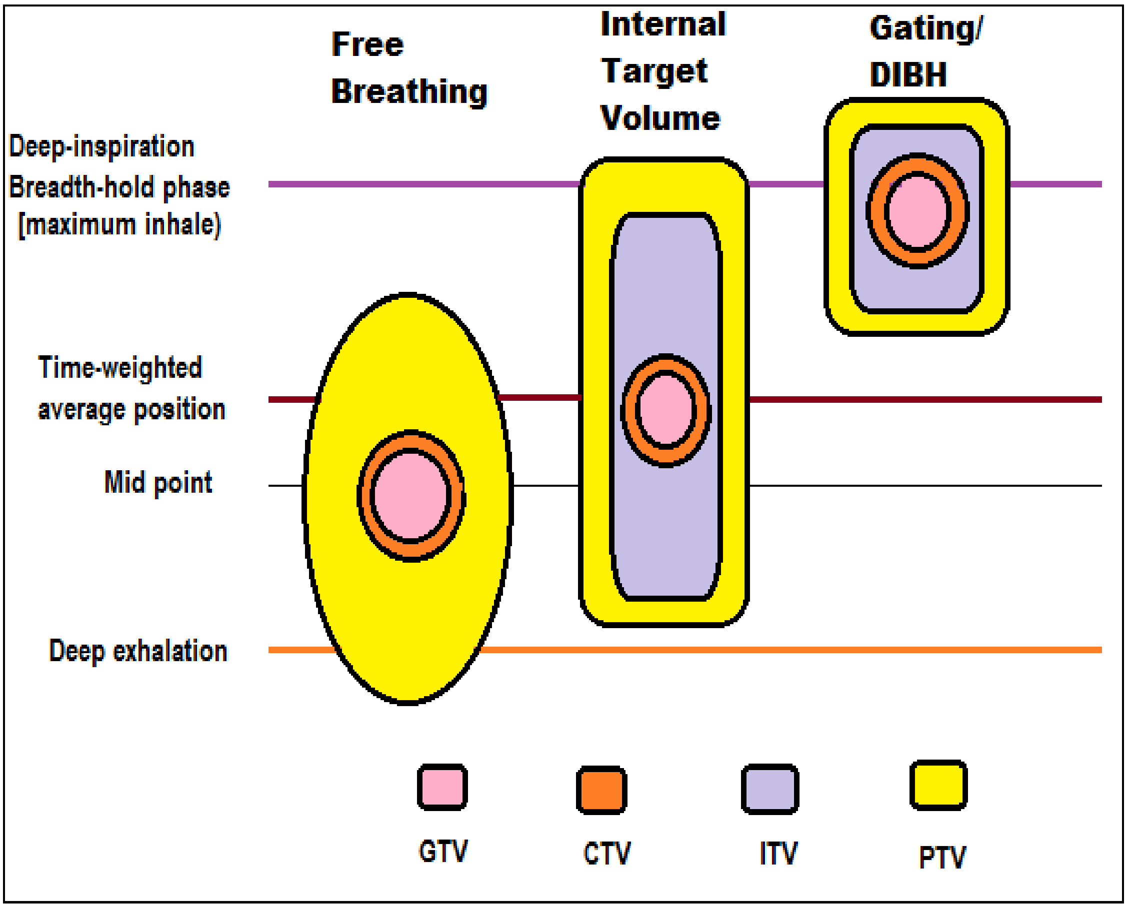

Figure. 1 Concept of ITV for motion management

4D Imaging Techniques

Significance of 4D imaging in motion management

The drawback of 3D conformal radiotherapy (3DCRT) is that more margin has to be given to adequately cover the target, thereby irradiating more normal tissues.[9] This results in high toxicity and limits the overall dose to the target. Thus 4DRT, guided by 4D-imaging, precisely localizes the target in space and time to maximize dose to the target and minimize the dose to the normal structures.[10] Advancement in cardiac imaging employed techniques to reduce the motion artifacts and this has been extended to 3DCT diagnostic image sets of the thorax and abdomen to tackle the respiration artifacts. [11,12] Although this resolution of artifacts in diagnostic images is good, it is not quantitatively defined. Quantitative correction of image information is necessary for RT imaging which is incorporated into planning and delivery. Thus, 4D imaging has evolved specifically to capture this information for radiotherapy applications.[13]

4DCT and Motion Management

Two types of 4D acquisition are available viz. Prospective and retrospective methods. In the prospective method, the images are acquired at a specific breathing cycle. The algorithm picks an appropriate breathing state, where suitable scans are acquired with minimal or negligible noise and reconstructed to yield a better 3D motion of the scanned area. In the retrospective method, several data sets are acquired at each breathing cycle. Thus, the breathing cycle has to be captured synchronously over the entire scan area. The entire breathing cycle is divided into 8-12 states, and each breathing state has a motion-free 3D volume data set. This type of 4D acquisition is more time consuming than the prospective scan but has improved quality. Each data set could be processed separately, or could be combined to yield a 4DCT. [14-16] This gives a clear picture of movement of target or gross tumor at different breathing states. Thus, a 4DCT is widely utilized to generate an ITV in radiotherapy, especially for stereotactic body radiation therapy (SBRT). A similar retrospective method is also employed in PET scans to yield a 4D PET. [17]

Breathing Consistency:

Breathing motion for any patient is generally inconsistent and needs to be measured to give a meaningful waveform. It may vary with amplitude from time to time and measurement of respiratory motion is necessary for planning. Many studies have evaluated the variables in respiratory motion. [18-20] The resting time at ‘end expiration’ is slightly higher compared to other phases of respiration and hence it is relatively stable. Thus, the end-expiration phase is less affected by the inconsistencies and useful for contouring and planning. However, the lung volume at this phase is very low compared to the deep-inspiration phase.[21] When lung is accounted for during the end-expiration phase, the percentage of lung receiving any dose will be higher. In contrast, one of the studies for pancreatic cancer, the dose to the duodenum is less when planned at the end-expiration phase.[22]

2. Materials and Methods

Large margins lead to unnecessary exposure of normal tissues near the target. The effects of tumor motion have to be limited to minimize normal tissue complications.[23] There is also a possibility that the target volume may come out of the treatment margin when there are adverse respiratory changes (couch, sneeze etc.). Such changes can only be addressed when breathing is monitored.

Surrogates and Motion Tracking Methods

4D patient monitoring for radiation therapy requires external or internal markers to monitor the consistency of the breathing motion. These markers provide adequate information of time-amplitude in synchrony with the breathing motion. [24-26] Common external markers employed for these purposes are:

1. Infrared markers placed on the thorax or abdomen
2. Spirometer to measure the lung volume
3. Thermometer based sensors to measure the external and internal air temperatures (nasal)
4. Pressure sensor in abdomen region to measure diaphragm pressure

Internal markers placed inside the body is labor some, time consuming and chances are there that we may lose or miss the information. Reports show that deformable image registration could be employed to segregate the inspiration and expiration scan stages with less than 5% error. But there are substantial image irregularities if the breathing motion is not uniform.[27]

To minimize the respiration induced motion, some centers have employed abdominal compression. It required application of pressure in the lower abdomen region to restrict the motion of lung and liver lesions. With no compression, medium compression and high compression the mean tumor motions were 13.6mm, 8.3mm and 7.2mm respectively.[28] Thus a significant motion control is observed in superior-inferior direction. In another study the liver motion is monitored and they observed that the liver motion is arrested within 5 mm in all directions. [29,30] Another study by Ecclles et al., 2011[31] has concluded that significant decrease in motion for 40% of patients. Apart from liver lesions, abdominal compression also helps lower lobe lung lesions for motion restriction and it is statistically significant when compared without compression.[32] Active breathing control (ABC) is another motion reducing method. In this method, the breathing is temporarily stopped for a comfortable period within which the radiation treatment is performed. Reproducibility is key to this method. A computer-controlled device is used to monitor the flow of air to the patient through the mouth and nasal breathing is stopped. Gagel et al have reported significant reduction of motion in the chest region when ABC is used.[33] Reproducible lung (1%) and liver (6%) volumes were observed by Wong et al with ABC.[34]

3. Results and Discussion

Breath Hold technique

In this technique, the patient is trained to hold the breadth mostly at the end expiration phase or during deep inspiration. Thus, the patient is made to hold the breadth voluntarily by arresting the tumor motion at a particular phase for a comfortable time. This breadth-hold is performed uniformly during CT image acquisition, verification image acquisition and during treatment delivery. To maintain the consistency of the breadth-hold, it is monitored using different methods. The most commonly used method is infra-red based markers and a camera system to capture the motion of the marker in real-time. This marker is placed either on the chest region or on the abdomen region to track the motion as shown in figure 2, thereby forming a wave pattern.[35] Once the breathing waveform is obtained during the CT acquisition, this is used as a baseline value for subsequent treatments. Optimum window in the waveform is chosen for treatment delivery. Breadth-hold can also be achieved using spirometers similar to ABC discussed previously. Other methods to track the breadth-hold are mechanical devices on torso, thermal sensors near nostrils, tracking the implanted fiducials using fluoroscopy etc.[36,37] These respiratory monitoring tools help to maintain the reproducibility of the breath-hold pattern and thus gives confidence for SBRT and SRS treatments.[38] End expiration phase is considered most stable and reproducible, but patients may find it difficult to hold it repeatedly.[39] To improve the lung DVH, end inspiration (deep inspiration) is useful especially for breast and lung treatments.[40]

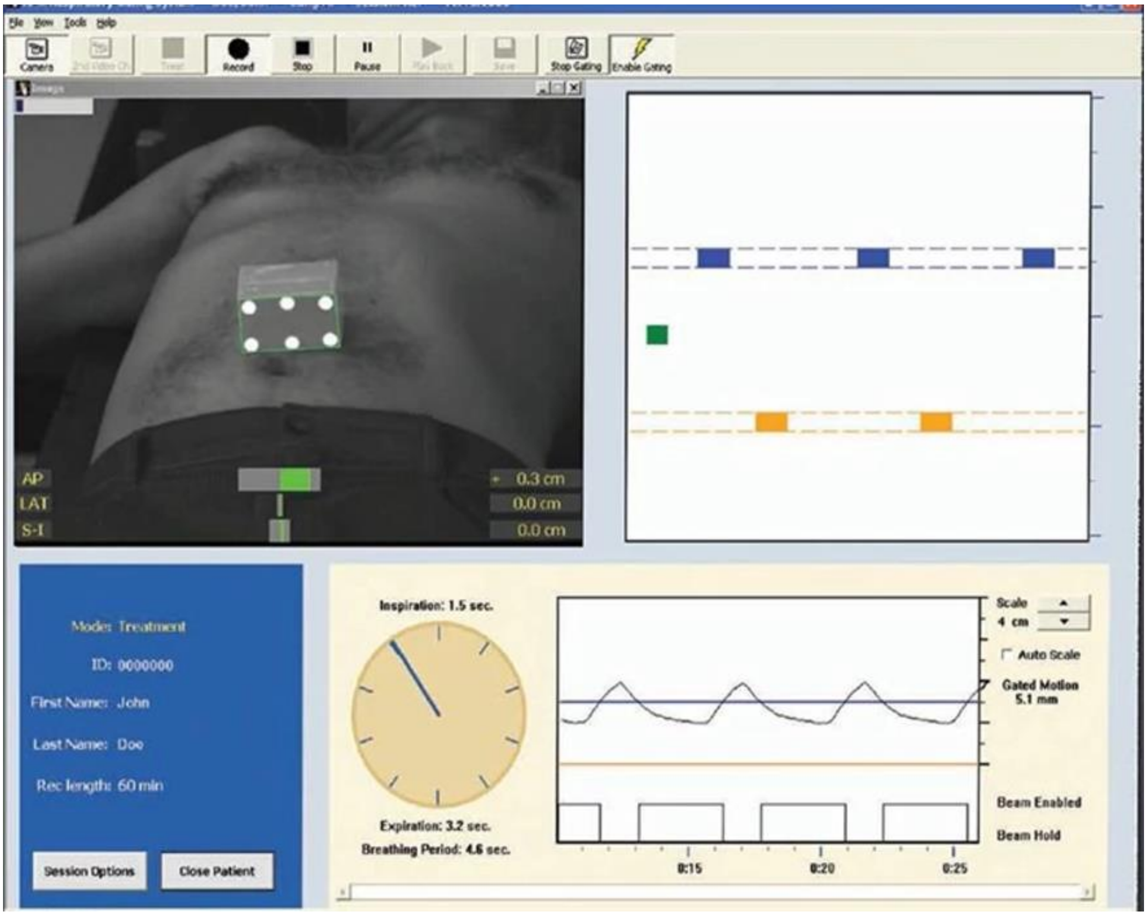

Figure. 2 Infra-red surrogate markers placed in upper abdomen for breath-hold treatment

Gating and tumor tracking

A few instances may not require a 4D information but gated3D volume information of over one or optimum breathing state. For example, for radiation therapy of left-sided breast cancer 3DCT is required in a deep inspiration state for planning and dose reporting. Although this information is a subset of 4DCT, imaging only at a particular phase will save time and reduce the imaging dose to the patient.[41] The process of gated imaging involves capturing the breathing cycle using external or internal markers and triggering the scan only during the required breathing state. Delineation of volumes and planning is done using this CT data set.[42] Also, before the start of the radiation treatment, the verification image is acquired in this gating phase only. The selection of gating window levels could be broad or narrow. A broad window level makes the treatment faster where the beam will be on as long as the patient is holding the big window level, but there is uncertainty in the treatment delivery. If a narrow window level is selected the tumor could be targeted precisely, but the treatment time could be made longer. This is because the patient has to maintain the narrow breathing state for a long time which is practically difficult. Thus, an optimum window level must be selected and the patient has to be trained appropriately. Refer figure 3 for phase-wise gating technique. Also, a Gated CT may save time while gated Cone beam computed tomography (CBCT) will require more time as the volumetric imaging requires a particular breathing window to acquire the images.[43]

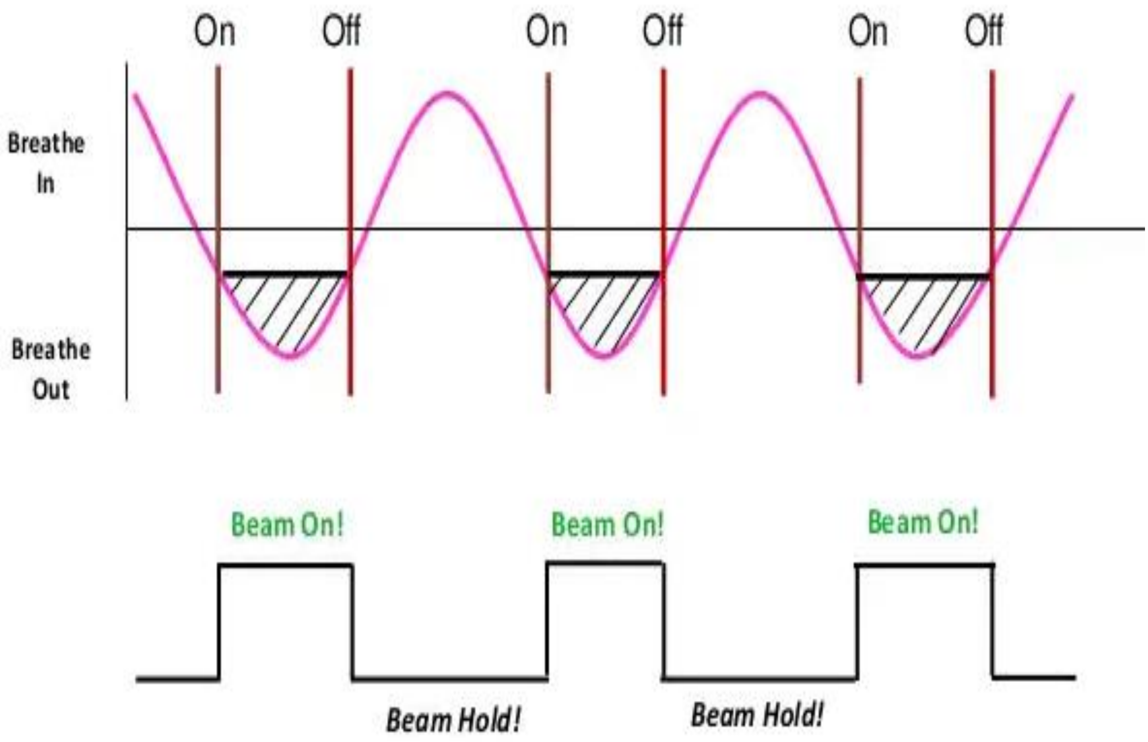

Figure. 3 Example for a phase-based gating technique

Tumor tracking utilizes dynamic multi-leaf collimators (DMLCs) to shape and align based on the movement of the tumor in real time. Thus, the apertures of DMLCs are continuously altered to shape the tumor in addition to the beam modulation. This is achieved for both static IMRT deliveries and volumetric modulated arc therapy (VMAT). Keall et al have reported an improvement in dose distribution with tumor tracking.[44] They tracked the tumor position electromagnetically to shape the tumor using MLCs in real-time. Varian's Real-time positioning management (RPM) gating system helps us to track the tumor using MLCs in real time.[45] Also, the gamma passing criteria is higher for plans with tumor tracking using DMLCs. Eleckta, also uses motion compensated VMAT delivery using Agility™.[46] Accuracy Oncology used Synchrony™ Respiratory tracking system. This creates a model of target motion using fiducials implanted in the tumor using orthogonal images. This model is then used to track the tumor during treatment using Cyberknife robotic linear accelerator. [38,47]

Breathing pattern consistency is key to any type of motion management strategies. Thus, coaching a qualifying patient for relevant strategy helps us to achieve better results. Coaching the patient is very much required when an external surrogate placed between zyphoid notch to the abdomen.[48] The internal markers such as implantation of fiducial(s) in tumors are invasive and coaching is not relevant. Correlation of abdominal wall and tumor position has improved with audio coaching as per Nakamura et al., 2009.[49] Similar better results were achieved for Goosen et al., 2014 and Mageras et al., 2001 with coaching. [50,51] Video coaching is also an effective way to achieve the reproducibility of the breathing motion. One study conducted by Onishiet al., 2010 found that the consistency of lung motion on an average was 2.0mm and 4.2mm with and without video coaching respectively.[37] Thus either audio or video coaching for breathing helps to achieve reliable dose delivery.

4D Radiation therapy

Radiation therapy is primarily based on 3D volume which is basically acquired in one particular time. This 3D image set is static and does not account the intra-fractional motion within the patient. Conformal radiation therapy thus does not account for the errors from patient setup and organ motion. The GTV, and related organs change its size and shape due to the intrafractional motion. This information is available only on a 4DCT image. In addition to this the interfractional variation of patient setup is also not accounted for. This requires a real-time imaging and positional correction of daily treatment setup. Presently, On-board imaging (OBI) greatly reduces the interfraction variation but, the organ motion is still not accounted clinically. To compensate for this uncertainty, an additional margin has to be 'grown' which will account for both inter- and intra-fractional variations.

Treatment planning remains challenging for lung and lower abdomen regions for several reasons. Physics of radiation transport in low density areas, correction for heterogeneity, effect of motion on dose distribution, and physics of small field dosimetry for SBRT treatments in motion susceptible areas are some of the important challenges. There are several comprehensive reviews for planning and delivery for lung and upper abdomen regions. [52-55] Lateral scattering is more pronounced for lung tumors as their tissue density is low. The central axis tumor dose tends to reduce as the energy increases since the secondary electrons travel more in low density regions.[56] This problem is exaggerated when the tumor is subjected to motion. In case of small tumors, such as SBRT, there is loss of charged particle equilibrium laterally. Thus, selection of dose calculation algorithms for lung regions, especially for small tumors is challenging. It has been reported that the pencil beam algorithm is poor in dose prediction as it does not account for transport for secondary electrons. AAPM task group 101 recommends convolution-superposition or Monte-carlo based dose calculation algorithms for accurate dose prediction.[57]

A maximum intensity projection (MIP) image can be generated from an image data set for each phase of the breathing cycle. Automatic tools are available to generate these MIP images as a 4DCT dataset is available.[58] MIP represents the maximum intensity value for each dataset acquired in a particular phase. The summation of MIP images helps us to generate the GTV accurately and is mostly used for lung tumors only. Studies have shown that it is not effective for tumors near the diaphragm or in the upper abdomen.[59] There is always a question of how many CT phases are required to generate accurate GTV motion. Studies have compared the GTV and ITV volumes using 2,4,8,10 seconds datasets acquired during the entire respiration cycle. Investigators have found that there is no statistical difference in generation of ITV when the respiration cycle is divided into 4 or 10.[60] In another study for pancreatic cancer, just 3 phases of CT data is sufficient to accurately (95%) generate ITV when the motion is less than 8mm.

Conclusion

For lung and abdominal tumors, especially for SBRT treatments, a motion study must be performed using 4DCT, 4D PET and/or 4D MRI. Tumor and critical organ motion must be incorporated into the planning contours for all acquired phases. For lung and abdominal targets, end expiration phase can be used for gated treatments and mid-ventilation phase can be used if treated with free breathing. Any anatomic changes, intra-fraction motion and daily setup variation must be accounted for in PTV margin. Intra-fraction motion tends to increase when the treatment time exceeds 30 minutes and this can be mitigated with repetition of imaging during the treatment. Any residual tumor motion must be included with the ITV even after the employment of motion handling methods. Coaching the patient is essential for any type of motion management strategy. It improves the correlation of internal organ motion and the external marker. Amplitude gating is simple and more accurate than phase gating. Audio coaching is sufficient for amplitude gating.

Monte-carlo or convolution superposition algorithm is always preferred to pencil beam algorithms for low density tissues. Heterogeneity correction must be incorporated for dose calculation. Daily image guidance (CBCT, CT-on rails or 4D MRI) is required. Respiratory motion must always be monitored during the treatment and assist the physicians to intervene the treatment for breathing discrepancies. Thus, our work provides recommendations for performing SBRT treatment for lung and upper abdominal tumors and to incorporate them clinically.

Recommendation

Motion Management has been a big challenge in Radiotherapy, with many uncertainties in imaging, contouring, setup, and treatment. It is important to understand the advantages and limitations of various motion management techniques as they influence the treatment outcome, which is critical in the Thorax and Abdomen.

References:

4. Benchetrit G. Breathing pattern in humans: Diversity and individuality. Respir Physiol. 2000;122:123–29. PubMed PMID: 10967339.
5. Keall PJ, Mageras GS, Balter JM, Emery RS, Forster KM, Jiang SB, et al. The management of respiratory motion in radiation oncology report of AAPM Task Group 76. Med Phys. 2006;33:3874-900. PubMed PMID: 17089851.
6. Balter JM, Lam KL, McGinn CJ, Lawrence TS, Ten Haken RK. Improvement of CT-based treatment-planning models of abdominal targets using static exhale imaging. Int J Radiat Oncol. 1998;41:939–43. PubMed PMID: 9652861.
7. Davies SC, Hill La, Holmes RB, Halliwell M, Jackson PC. Ultrasound quantitation of respiratory organ motion in the upper abdomen. Br J Radiol. 1994;67:1096–102. PubMed PMID: 7820402.
8. Shirato H, Seppenwoolde Y, Kitamura K, Onimura R, Shimizu S. Intrafractional Tumor Motion: Lung and Liver. Semin Radiat Oncol. 2004;14:10-8. PubMed PMID: 14752729.
9. Shirato H, Onimaru R, Ishikawa M, Kaneko JI, Takeshima T, Mochizuki K et al. Real-time 4-D radiotherapy for lung cancer. Cancer Sci. 2012;103:1–6. PubMed PMID: 21954991.
10. Kachelriess M, Ulzheimer S, Kalender WA. ECG-correlated imaging of the heart with subsecond multislice spiral CT. IEEE Transactions on Medical Imaging. 2000;19:888–901.
11. Landberg, T., Chavaudra, J., Dobbs, H. ICRU Report 62: Prescribing, Recording, and Reporting Photon Beam Therapy (Supplement to ICRU Report 50). International Commission on Radiation Units and Measurements; Bethesda, Maryland: 1999.
12. Ekberg L, Holmberg O, Wittgren L, Bjelkengren G, Landberg T. What margins should be added to the clinical target volume in radiotherapy treatment planning for lung cancer? Radiother Oncol. 1998;48:71–77. PubMed PMID: 9756174.
13. Chang JY, Dong L, Liu H, Starkschall G, Balter P, Mohan R, et al. Image-guided radiation therapy for non-small cell lung cancer. J Thorac Oncol. 2008;3:177–86. PubMed PMID: 18303441.
14. Xing, L., Thorndyke, B., Schreibmann, E., Yang, Y., Li, T.F., Kim, et al. Overview of image-guided radiation therapy. Med Dosim. 2006;31:91-112. PubMed PMID: 16690451.
15. Sonke, J.-J., Zijp, L., Remeijer, P., and van Herk, M. Respiratory correlated cone beam CT. Med Phys. 2005;32:1176-86. PubMed PMID: 15895601.
16. Pan, T. Motion artifacts and correction techniques in PET/CT. In: Khalil, M. editor. Basic Science of PET Imaging. Springer, Cham; 2017. p. 379-96.
17. Endo, M., Tsunoo, T., Kandatsu, S., Tanada, S., Aradate, H., and Saito, Y. Four-dimensional computed tomography (4D CT) – Concepts and preliminary development. Radiat Med. 2003;21:17-22. PubMed PMID: 12801139.
18. Olsen JR, Lu W, Hubenschmidt JP, Nystrom MM, Klahr P, Bradley JD, et al. Effect of novel amplitude/phase binning algorithm on commercial four-dimensional computed tomography quality. International Journal of Radiation Oncology Biology Physics. 2008;70:243-52. PubMed PMID: 18037590.
19. Guckenberger M, Weininger M, Wilbert J, Richter A, Baier K, Krieger T, et al. Influence of retrospective sorting on image quality in respiratory correlated computed tomography. Radiotherapy and oncology. 2007;85:223-31. PubMed PMID: 17854931.
20. Didierlaurent D, Ribes S, Batatia H, Jaudet C, Dierickx LO, Zerdoud S, et al. The retrospective binning method improves the consistency of phase binning in respiratory-gated PET/CT. Physics in Medicine & Biology. 2012;57:7829-41. PubMed PMID: 23135238.
21. Ozhasoglu C, Murphy MJ. Issues in respiratory motion compensation during external-beam radiotherapy. Int J Radiat Oncol Biol Phys. 2002;52:1389–99. PubMed PMID: 11955754.
22. Ruan D, FesslerJa, Balter JM, Keall PJ. Real-time profiling of respiratory motion: baseline drift, frequency variation and fundamental pattern change. Phys Med Biol. 2009;54:4777–92. PubMed PMID: 19622852.
23. Stock M, Kontrisova K, Dieckmann K, Bogner J, Poetter R, Georg D. Development and application of a real-time monitoring and feedback system for deep inspiration breath hold based on external marker tracking. Med Phys. 2006;33:2868–77. PubMed PMID: 16964863.
24. Wolfelschneider J, Brandt T, Lettmaier S, Fietkau R, Bert C. Quantification of an external motion surrogate for quality assurance in lung cancer radiation therapy. Biomed Res Int. 2014;2014:595430. PubMed PMID: 25525599.

25. Taniguchi CM, Murphy JD, Eclov N, Atwood TF, Kielar KN, Christman-Skieller C, et al. Dosimetric analysis of organs at risk during expiratory gating in stereotactic body radiation therapy for pancreatic cancer. Int J Radiat Oncol Biol Phys. 2013;85:1090–5. PubMed PMID: 23273994.
26. Ahn S, Yi B, Suh Y, Kim J, Lee S, Shin S, et al. A feasibility study on the prediction of tumour location in the lung from skin motion. Br J Radiol. 2004;77:588–96. PubMed PMID: 15238406.
27. Lu, W., Parikh, P. J., Hubenschmidt, J. P., Bradley, J. D., and Low, D. A. A comparison between amplitude sorting and phase-angle sorting using external respiratory measurement for 4D CT. Med Phys 2006;33:2964-74. PubMed PMID: 16964875.
28. Wink, N. M., Panknin, C., and Solberg, T. D. Phase versus amplitude sorting of 4D-CT data. J Appl Clin Med Phys. 2006;7:77-85. PubMed PMID: 16518319.
29. Kawakami, Y., Suga, K., Yamashita, T., Iwanaga, H., Zaki, M., and Matsunaga, N. Initial application of respiratory-gated 201Tl SPECT in pulmonary malignant tumors. Nucl Med Commun. 2005;26:303-13. PubMed PMID: 15753789.
30. Xu, S., Taylor, R. H., Gabor, F., and Cleary, K. Lung deformation estimation and four-dimensional CT lung reconstruction. Acad Radiol. 2006;13:1082-92. PubMed PMID: 16935720.
31. Sonke, J.-J., Zijp, L., Remeijer, P., and van Herk, M. Respiratory correlated cone beam CT. Med Phys. 2005;32:1176-86. PubMed PMID: 15895601.
32. Heinzerling JH, Anderson JF, Papiez L, Boike T, Chien S, Zhang G, et al. Four-dimensional computed tomography scan analysis of tumor and organ motion at varying levels of abdominal compression during stereotactic treatment of lung and liver. Int J Radiat Oncol Biol Phys. 2008;70:1571–8. PubMed PMID: 18374231.
33. Wunderink W, Méndez Romero A, de Kruijf W, de Boer H, Levendag P, Heijmen B. Reduction of respiratory liver tumor motion by abdominal compression in stereotactic body frame, analyzed by tracking fiducial markers implanted in liver. Int J Radiat Oncol Biol Phys. 2008;71:907–15. PubMed PMID: 18514783.
34. Eccles CL, Patel R, Simeonov AK, Lockwood G, Haider M, Dawson La. Comparison of liver tumor motion with and without abdominal compression using cine-magnetic resonance imaging. Int J Radiat Oncol Biol Phys. 2011;79:602–8. PubMed PMID: 20675063.
35. Bouilhol G, Ayadi M, Rit S, Thengumpallil S, Schaerer J, Vandemeulebroucke J, et al. Is abdominal compression useful in lung stereotactic body radiation therapy? A 4DCT and dosimetric lobe-dependent study. Phys Med. 2013;29:333–40. PubMed PMID: 22617761.
36. Gagel B, Demirel C, Kientopf A, Pinkawa M, Piroth M, Stanzel S, et al. Active breathing control (ABC): Determination and reduction of breathing-induced organ motion in the chest. Int J Radiat Oncol Biol Phys. 2007;67:742–49. PubMed PMID: 17197133.
37. Wong JW, Sharpe MB, Jaffray Da, Kini VR, Robertson JM, Stromberg JS, et al. The use of active breathing control (ABC) to reduce margin for breathing motion. Int J Radiat Oncol Biol Phys. 1999;44:911–9. PubMed PMID: 10386650.
38. Kubo HD, Hill BC. Respiration gated radiotherapy treatment: a technical study. Phys Med Biol. 1996;41:83–91. PubMed PMID: 8685260.
39. Glide-Hurst CK, Chetty IJ. Improving radiotherapy planning, delivery accuracy, and normal tissue sparing using cutting edge technologies. J Thorac Dis. 2014;6:303–18. PubMed PMID: 24688775.
40. Onishi H, Kawakami H, Marino K, Komiyama T, Kuriyama K, Araya M, et al. A simple respiratory indicator for irradiation during voluntary breath holding: a one-touch device without electronic materials. Radiology. 2010;255:917–23. PubMed PMID: 20501729.
41. Murphy MJ, Martin D, Whyte R, Hai J, Ozhasoglu C, Le QT. The effectiveness of breath-holding to stabilize lung and pancreas tumors during radiosurgery. Int J Radiat Oncol Biol Phys. 2002;53:475–82. PubMed PMID: 12023152.
42. Vedam SS, Keall PJ, Kini VR, Mohan R. Determining parameters for respiration-gated radiotherapy. Med Phys. 2001;28:2139–46. PubMed PMID: 11695776.
43. Mageras GS, Yorke E. Deep inspiration breath hold and respiratory gating strategies for reducing organ motion in radiation treatment. Semin Radiat Oncol. 2004;14:65–75. PubMed PMID: 14752734.
44. Langen KM, Jones DT. Organ motion and its management. Int J Radiat Oncol Biol Phys. 2001;50:265–78. PubMed PMID: 11316572.
45. Brandner ED, Wu A, Chen H, Heron D, Kalnicki S, Komanduri K, et al. Abdominal organ motion measured using 4D CT. Int J Radiat Oncol Biol Phys. 2006;65:554–60. PubMed PMID: 16690437.
46. Shen S, Duan J, Fiveash JB, Brezovich IA, Plant BA, Spencer SA, et al. Validation of target volume and position in respiratory gated CT planning and treatment. Med Phys. 2003;30:3196–205. PubMed PMID: 14713086.
47. Keall PJ, Colvill E, O'Brien R, Ng JA, Poulsen PR, Eade T, et al. The first clinical implementation of electromagnetic transponder-guided MLC tracking. Med Phys. 2014;41:020702. PubMed PMID: 24506591.

48. Falk M, af Rosenschöld PM, Keall P, Cattell H, Cho BC, Poulsen P, et al. Real-time dynamic MLC tracking for inversely optimized arc radiotherapy. Radiother Oncol. 2010;94:218–23. PubMed PMID: 20089322.
49. Davies, Ga, Clowes, P., Bedford, JL., Evans, PM., Webb, S., Poludniowski, G. An experimental evaluation of the Agility MLC for motion-compensated VMAT delivery. Phys Med Biol. 2013;58:4643–57. PubMed PMID: 23780400.
50. Dawson, La, Sharpe, MB. Image-guided radiotherapy : rationale, benefits, and limitations. Lancet Oncol. 2006;7:848-58. PubMed PMID: 17012047.
51. Liu HH, Koch N, Starkschall G, Jacobson M, Forster K, Liao Z, et al. Evaluation of internal lung motion for respiratory-gated radiotherapy using MRI: Part I - correlating internal lung motion with skin fiducial motion. Int J Radiat Oncol Biol Phys. 2004;60:1459–72. PubMed PMID: 15590177.
52. Nakamura M, Narita Y, Matsuo Y, Narabayashi M, Nakata M, Sawada A, et al. Effect of audio coaching on correlation of abdominal displacement with lung tumor motion. Int J Radiat Oncol Biol Phys. 2009;75:558–63. PubMed PMID:19735881.
53. Goossens S, Senny F, Lee JA, Janssens G, Geets X. Assessment of tumor motion reproducibility with audio-visual coaching through successive 4D CT sessions. J Appl Clin Med Phys. 2014;15:47–56. PubMed PMID: 24423834.
54. Mageras GS, Yorke E, Rosenzweig K, Braban L, Keatley E, Ford E, et al. Fluoroscopic evaluation of diaphragmatic motion reduction with a respiratory gated radiotherapy system. J Appl Clin Med Phys. 2001;2:191– 200. PubMed PMID: 11686740.
55. JeremicB, Advances in Radiation Oncology in Lung Cancer. In: Brady L W, Heilmann H P, Molls M. editors. Springer; Berlin: 2005.
56. Slotman BJ, Lagerwaard FJ, Senan S. 4D imaging for target definition in stereotactic radiotherapy for lung cancer. Acta Oncol. 2006;45:966–72. PubMed PMID: 16982565.
57. Scorsetti M, Clerici E, Comito T. Stereotactic body radiation therapy for liver metastases. J Gastrointest Oncol. 2014;5:190–7. PubMed PMID: 24982767.
58. Solberg TD, Balter JM, Benedict SH, Fraass BA, Kavanagh B, Miyamoto C, et al. Quality and safety considerations in stereotactic radiosurgery and stereotactic body radiation therapy: Executive summary. Pract Radiat Oncol. 2012;2:2–9. PubMed PMID: 25740120.
59. Arnfield MR, Siantar CH, Siebers J, Garmon P, Cox L, Mohan R. The impact of electron transport on the accuracy of computed dose. Med Phys. 2000;27:1266-74. PubMed PMID: 10902555.
60. Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys. 2010;37:4078-101. PubMed PMID: 20879569.
61. Rietzel E, Liu AK, Chen GTY, Choi NC. Maximum-intensity volumes for fast contouring of lung tumors including respiratory motion in 4DCT planning. Int J Radiat Oncol Biol Phys. 2008;71:1245–52. PubMed PMID: 18472367.
62. Bradley JD, Nofal AN, El Naqa IM, Lu W, Liu J, Hubenschmidt J, et al. Comparison of helical, maximum intensity projection (MIP), and averaged intensity (AI) 4D CT imaging for stereotactic body radiation therapy (SBRT) planning in lung cancer. Radiother Oncol. 2006;81:264–8. PubMed PMID: 17113668.
63. Yeo S-G, Kim ES. Efficient approach for determining four-dimensional computed tomography based internal target volume in stereotactic radiotherapy of lung cancer. Radiat Oncol J. 2013;31:247–51. PubMed PMID: 24501714